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A PRELIMINARY REPORT ON THE OSTEOGENIC POTENTIAL OF A BIODEGRAD--ETC(U)
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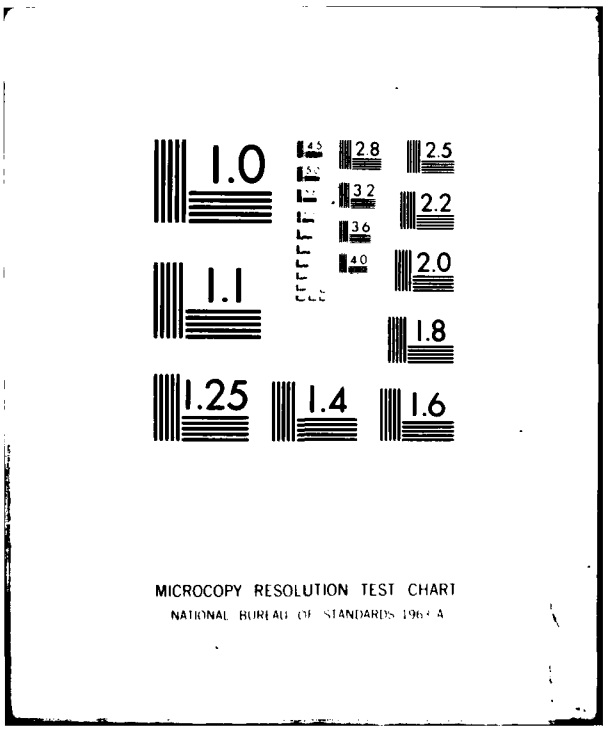
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A biodegradable copolymer of 50:50 polylactide:polyglycolide was prepared for implantation into experimentally created osseous defects in the tibias of 25 rats. Similarly prepared defects were made in the humeri and these did not receive copolymer implants. At 7, 14, 21, 28, and 42 days five animals were sacrificed and the implant and untreated sites were evaluated by gross visual inspection and by histologic examination using a Zeiss Videoplan Image Analysis System with Osteoplan for the quantitation of bone morphometrics. When compared with bony defects that were not treated with the biodegradable copolymer implant

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the implant sites displayed a slightly accelerated healing response rate at 7 days ($p<0.01$), a slightly accelerated response rate at 14 and 21 days ($p<0.005$), and a similar healing response rate at 28 and 42 days ($p<0.01$). The copolymer was highly tissue tolerant throughout the period of the investigation.

A PRELIMINARY REPORT ON THE OSTEOGENIC POTENTIAL OF A BIODEGRADABLE COPOLYMER OF POLYLACTIDE:POLYGLYCOLIDE (PLA:PGA)

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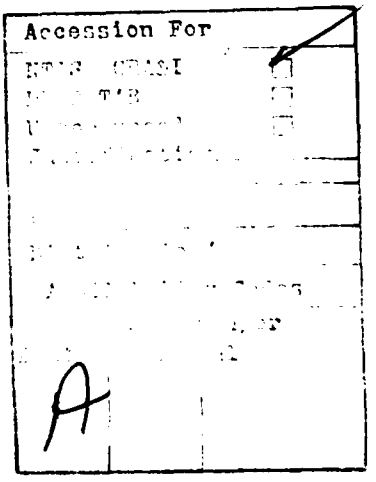

A PRELIMINARY REPORT ON THE OSTEOGENIC POTENTIAL OF A BIODEGRADABLE COPOLYMER OF POLYLACTIDE:POLYGLYCOLIDE

SYNOPSIS

A biodegradable copolymer of 50:50 polylactide:polyglycolide was prepared for implantation into experimentally created osseous defects in the tibias of 25 rats. Similarly prepared defects were made in the humeri of the same rats and these defects did not receive copolymer implants. Upon sacrifice, both the implant treated and untreated sites of the experimentally produced osseous defects were evaluated by gross appearance and by histomorphometric examination using a Zeiss Videoplan Image Analysis System with Osteoplan™ (vers 4.1). The animals were evaluated in groups of five at 7, 14, 21, 28, and 42 days. When compared with bony defects that were not treated with the biocompatible, biodegradable copolymer implant, the implant sites displayed an accelerated rate of healing at 7, 14, 21, and 28 days ($p<0.001$). However, a similar healing response rate was observed at 42 days ($p<0.25$-0.1). No adverse host tissue responses were observed histologically.

KEY WORDS Biodegradable Copolymer; Polylactic and Polyglycolic Acids; Osteogenic; Osseous Wound Repair; Accelerated Bony Healing.

INTRODUCTION

The alpha-polyesters, polylactide and polyglycolide, have been investigated for use as suture and implant materials for the repair of a variety of soft tissue and osseous wounds.[1-7] Implanted polymers and copolymers of polylactide and polyglycolide were expected to function in a supportive role, to undergo hydrolytic scission to form nontoxic, excretable metabolites, and to be ultimately replaced by the host's contiguous tissue. Getter[4] observed that a homopolymer of lactic acid, when used in dogs for mandibular fracture repair, had partially degraded after six weeks and was completely resorbed after thirty-two weeks with the fracture sites being indistinguishable from the adjacent bone areas. Cutright[5] employed a similar homopolymer implant for the repair of blowout fractures of the orbital floor in monkeys. After thirty-eight weeks it was found that the implants were being tolerated well but had not been completely resorbed, although phagocytosis of polymer fragments was occurring. At this time there is no information in the literature about the osteogenic potential of a 50:50 copolymer of polylactide:polyglycol (PLA:PGA) to induce bony wound healing. It was the purpose of this study, therefore, to evaluate the healing capacity of prepared osseous wounds treated with the biocompatible, biodegradable copolymer of 50:50 PLA:PGA compared with nontreated control bony wounds.

METHODS AND MATERIALS

A commercially synthesized copolymer of 50:50 PLA:PGA (50:50 poly (L (-) lactide co-glycolide), having a viscosity of 0.92 dl/g

as measured in hexafluoroisopropanol at 30C, corresponding to a weight-average-molecular weight of approximately 80,000 Daltons, was solubilized in methylene chloride at a 1:12.5 weight:volume ratio. Anhydrous methanol (1:1) was added to this liquid suspension to precipitate a milky-white gelatinous mass which was then placed into prepared wells (2.0 mm X 1.25 mm) in a Teflon mold. The viscous, milky-white copolymer mass was gently forced into the prepared wells using a supple Teflon spatula and then was placed in a lyophilizer chamber at 30C and a pressure of 0.005 mm of mercury for 48 hours. After 48 hours each copolymer preparation was designated as an implant plug (Figure 0A and 0B) and all plugs were sterilized in ethylene oxide and stored in a dessicator.

Using sodium pentobarbital, USP (Pentobarbital Sodium), 25 adult Walter Reed strain of rats (random male and female) were anesthetized by IP injection at a dose of 3 to 5 mg/100 mg of body weight. Each tibia was prepared for a copolymer implant and each humerus was prepared as a control. The areas over the tibias and the humeri were shaved and scrubbed with povidone iodine, NF (Betadine®) for three to five minutes. An incision 1 cm in length was made on the anteriolateral surface of each tibia and humerus and soft tissue was reflected down to bone to expose the broadest area of the diaphysis. A hole was made completely through the cortical plate and into the medullary cavity using a bone trephine (OD = 1.95 mm) and sterile water coolant. An implant was placed in each tibia and

the humeri holes were left void to serve as controls. In this laboratory, histomorpometric evaluation of osseous healing rates of bony wounds in rat tibias and humeri did not reveal any significant differences in the rate of osseous repair. All surgical sites were appropriately sutured and the animals were returned to their individually marked cages. At 7, 14, 21, 28, and 42 days five animals were sacrificed by administration of an overdose of sodium pentobarbital. Gross examination was made of the implant and control areas after surgical removal of the overlying soft tissues. A bone saw was then used to remove the implant and control sites from the contiguous bone and at least 5 mm of host bone remained to encompass these zones. The retrieved specimens were fixed in 10% formalin. After decalcification for 18 hours in Bankuthy's medium, the specimens were prepared for hematoxylin and eosin staining.

Using bright field illumination and polarization microscopy[8] at a magnification of 200X, histomorphometric analysis was performed on a minimum of 100 histologic fields from both of the experimental (implant) and control sites from each animal. Therefore, a minimum of 200 fields for experimental and control areas were evaluated for each animal. Data from these evaluations from the five rats from each temporal group were combined and the pooled mean values ± standard deviations were calculated. A Student's t test $\left(t = \bar{x}_1 - \bar{x}_2 / \sqrt{\frac{\delta_1^2 \pm \delta_2^2}{n-1}}\right)$ was performed between the same histomorphometric variables of the same temporal group. The level of significance was determined based upon each t value.

RESULTS

Gross Examination

Control Sites

1. 7 to 14 days: Inspection revealed circular wounds that appeared to be filled with a reddish-brown soft tissue.
2. 21 days: Wounds were similar in configuration to the 7 and 14 day levels, with the exception that tissue in the wound bed appeared to be speckled with osteoid or osseous components.
3. 28 and 42 days: By 28 days it had become increasingly difficult to discern wound sites from contiguous bone. By 42 days all control wounds demonstrated complete osseous union.

Implant Sites

1. 7 days: Rather than the crisply shaped circular implant plug, an irregularly contoured implant was evident in the experimental site. The implant appeared to be firmly fixed in all the experimental sites. Reddish-brown soft tissue was apparent among the implant interstices.
2. 14 through 28 days: It became obvious as the experiment progressed that the copolymer implant was gradually hydrolyzing (breaking down) and that a whitish (osteoid?) tissue fill was filling the prepared wound zones. The implant remained firmly entrenched within the wound bed at all times.
3. 42 days: There appeared to be no gross evidence of the copolymer implant. Bony union appeared to have been achieved.

Histologic Examination

Control Sites

Histologic observation of the healing control sites revealed an unremarkable progression of normal endochondral bone formation. A typical callus developed and osteogenic cell proliferation resulted in a distinct collar of uniting tissue around the defect border. The more rapidly growing areas of the callus displayed chondrocytic differentiation at the early stages (7 through 21 days). As a capillary network developed and became steadily more advanced, vascular penetration into the carlilaginous sanctum occurred and osteoblastic cell populations became predominant. By 28 to 42 days numerous zones of osteoid and bony spicules had been replaced by rapidly coalescing trabeculae (Fig. 1). By 42 days a complete bony union had been achieved, albeit areas of immature bone were evident. Osteons were not present, indicating that at 42 days substantial union was still lacking.

Implant Sites

1. 7 days: The implant appeared as a wavy, heterogenous, and amorphous structure with infrequent lymphocytic infiltrate and a few polymorphonuclear cells (Fig. 2A). Host-cell activity was evident at the implant periphery; centrally, a minimal number of lymphocytes were observed. Juxtaposed to the copolymer implant-host bone boundary were zones of osteoid with frequent robust osteoblasts (Fig. 2B).
2. 14 and 21 days: The implants became increasingly more tenuous as the experiment continued. Observed at 14 days, and more dramatically apparent at 21 days, was the gradual

dissolution of the implant into multiple islands and peninsulas of material with osteoid-immature bone-copolymer intercalations (Fig. 3). Trabeculae with rimming osteoblasts became more predominant at 21 days than at 14 days (Fig. 4). Birefringence of the polyglycolide from hydrolytic scission of the implant was typical of the 21-day histologic picture. A robust periosteal callus was routinely seen by 21 days. Some specimens (Fig. 5) displayed remarkable fervor in their bony healing response.

3. 28 and 42 days: Implant copolymer was present at 42 days in the form of isolated, irregularly shaped small zones of birefringence. Osteoid and trabecular coalescence were evident at 28 and 42 days, despite remaining implant that had not been fully degraded. Capillary penetration and phagocytic cells were often closely associated with residual copolymer islands. Satisfactory callus formation resulted in complete obliteration of the wound defect by 42 days, and in several specimens this result was achieved at the 28-day level (Fig. 6). There was no indication of an inflammatory response in any of the implant specimens. Tissue tolerance of the implant copolymer was extremely favorable.

Histomorphometric Analysis

Using Student's t test there was a significant difference in the

pooled mean values between the same histomorphometric variables of the experimental and control sites for the 7, 14, 21, and 28 day temporal groups ($p<0.001$, or $p<0.03$ and 0.02 where noted in Table 1). At 42 days the pooled mean values for the same experimental and control variables tended to converge, with real differences diminishing. The level of significance varied from $p<0.1$-0.25, except as otherwise noted in Table 1. Standard deviations did not vary significantly throughout the experiment (Table 1).

DISCUSSION

In different experiments, Getter *et al.*[4] and Cutright *et al.*[5] determined that a homopolymer of lactic acid (PLA) could be used for selected types of osseous wound repair. These investigators also noted that PLA was observed histologically up to 38 weeks after implantation.[4] Several studies have shown histological evidence of homopolymers of glycolic acid (PGA) being present in soft tissue, varying from 50 to 120 days after implantation.[2,3] In a histologic study to plot copolymer and homopolymer degradation of PGA and PLA, Cutright *et al.*[5] determined that by varying the proportions of PLA to PGA, degradation rates could be varied from between 100 days to greater than 220 days. It was found that the homopolymers, PLA and PGA, persisted for the greatest time span, while the 25% PLA degraded most rapidly, followed in succession by 50% and 75% PLA.

Kulkarni *et al.*[10] investigated polylactide degradation *in vivo* using ^{14}C-labeled homopolymer. These workers compared the kinetics of degradation of the D,L- and L(-)-polymers and they established

that the D,L form degraded more rapidly. This property may be attributed to the high order of crystallinity of this form of polymer. The mechanical properties of homopolymers and copolymers of glycolide and lactide also vary directly with composition. The composition varies, according to Sinclair and Gynn, in relation to the degree of crystallinity.[11] The different optical activities (crystallinity) of the homopolymer/copolymer implants could logically explain the variable rates of degradation that have been reported. The degradation rate of a homopolymer/copolymer must be defined in terms of the polymer's optical activity. In the investigation undertaken in this laboratory, a 50:50 poly (L (-) lactide co-glycolide) implant was employed. Beginning at 7 days, and continuing until the experiment was terminated at 42 days, a haphazard breakdown was noted histologically. This observation could contrast markedly with a copolymer of a different optical activity or crystallinity. It is perhaps this factor that has led to some amount of disparity between studies, in terms of degradation rates of copolymers and homopolymers of lactides and glycolides. Also, different preparation techniques for fabrication of the copolymer implant could produce a variety of different physical properties. In this laboratory, a nondeformable, spongy morphology was achieved (Fig. 0A and 0B). In contrast, a glassy, dense structure could have been produced if such an attribute was desired. A hard, spongy architecture allows for rigid, stable bone fixation and permits host access to a vast molecular domain for hydrolytic scission and subsequent hard tissue ingress.

It would be germane at this time to mention briefly the manner by which the 50:50 PLA:PGA copolymer implant is degraded. Nonspecific hydrolytic scission of the copolymer chain results in the generation of lactic acid and glycolic acid residues. The lactic acid becomes incorporated into the tricarboxylic acid cycle and is consequently excreted by the lungs as CO_2. The glycolic acid molecules are acted upon by glycolate oxidase and are transformed into glyoxylate, which reacts with glycine transaminase and results in the formation of glycine. The glycine can be used for protein synthesis or for the synthesis of serine, which may be employed in the tricarboxylic acid cycle after transformation into pyruvate.

As copolymer dissolution by hydrolytic scission occurred, trabeculae replaced the degrading copolymer. The elements of bone formation or osseous repair that were histomorphometrically analyzed were observed to be in greater abundance and were present earlier in osseous wound sites treated with 50:50 PLA:PGA as compared with untreated control sites. It may be conjectured that the implant degradation products engendered an early osseous inductive response from the pluripotential cells of the cambial layer of the periosteum and endosteum. By 42 days, however, the rate at which bony repair took place in control wounds proceeded at a pace virtually equivalent to the experimental sites. Either the bone-inducing effect of the implant had diminished by 42 days, or the natural healing capacity of the animal had achieved parity with the implant site.

The presence of 50:50 PLA:PGA copolymer did not appear to adversely affect bone wound repair. There was evidence that the rate of early (7-28 days) osseous healing was actually accelerated. This compelling response will be further pursued in the laboratory because a copolymer employed for fracture fixation or for repair of bony discontinuity defects that could degrade in harmony with normal osseous healing would be ideal. If that same copolymer could also orchestrate an accelerated bone reparative process, than this would be superb.

CONCLUSION

Bone healing rate was assessed using selective morphometric variables that were quantitated using a Zeiss Image Analysis System with Osteoplan™ (vers 4.1). When compared with untreated bony wounds, the bony wounds where copolymer implants were inserted displayed an accelerated rate of bone healing at 7, 14, 21, and 28 days ($p<0.001$); however, a similar healing rate was observed at 42 days ($p<0.25$-0.1). Histologic evaluation did not indicate that there was any adverse host tissue response to the implant. Because stability in bony wound healing is a critical factor for successful bony repair, a biocompatible, biodegradable therapeutic agent that could hasten early osseous healing could mitigate against fragment migration and the sequella of nonunion.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on the Guide for Laboratory

Animal Facilities and Care, of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

Commercial materials and equipment are identified in this report to specify the investigative procedures. Such identification does not imply recommendation or endorsement or that the materials and equipment are necessarily the best available for the purpose. Furthermore, the opinions expressed herein are those of the author and are not to be construed as those of the U. S. Army Medical Department.

TABLE 1. HISTOMORPHOMETRIC ANALYSIS

DAYS: 7	7		14		21		28		42	
Pooled $\bar{x} \pm \delta$*	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control
VV	1.2±2.2	0.3±0.9	3.2±3.7	0.6±1.2	3.5±2.8	1.5±2.1	4.1±5.1	2.8±4.1	5.3±3.6	4.7±2.9
p	**		**		**		**		†	
SV	23.1±31.2	12.1±3.9	37.2±28.1	13.1±8.7	46.1±47.7	19.2±16.3	48.1±31.7	17.2±19.1	37.2±20.1	43.2±40.1
p	**		**		**		**		†	
D-TRAB	11.2±9.3	10.1±11.1	14.2±10.8	9.2±4.7	17.3±15.1	11.3±11.1	15.3±10.6	10.1±8.7	16.3±9.2	15.1±13.9
p	††		**		**		**		‡	
SV-UB	22.3±18.1	9.2±3.5	31.3±21.2	9.9±7.2	46.2±39.2	18.7±9.9	45.1±31.6	23.2±19.8	53.3±48.0	44.3±39.2
p	**		**		**		**		†	
OBI	5.2±2.1	1.2±0.5	12.3±4.2	2.1±1.1	11.6±4.1	2.1±1.0	13.7±6.1	7.8±2.1	12.1±8.1	13.3±9.8
p	**		**		**		**		‡	
OCI	1.1±0.9	0.9±0.3	3.1±1.8	0.7±0.2	1.9±1.2	0.9±0.3	2.3±0.9	1.9±0.9	1.3±0.8	2.1±1.3
p	‡‡		**		**		**		**	
OCL%	1.8±0.3	1.1±0.1	2.3±1.0	0.9±0.1	1.5±1.0	1.2±0.2	2.7±2.1	1.1±0.5	2.9±3.1	2.2±1.8
p	**		**		**		**		††	
V-L-UT	3.2±1.0	2.1±1.3	4.2±1.9	1.2±0.7	4.9±2.1	1.9±1.1	3.6±3.5	2.1±0.3	2.9±2.1	3.2±2.9
p	**		**		**		**		‡	
FIB%	4.1±3.2	1.8±0.9	3.2±2.2	2.1±0.8	12.6±4.3	2.9±1.3	13.3±7.1	1.1±0.7	9.1±7.6	4.7±3.7
p	**		**		**		**		**	

* $\bar{x} \pm \delta$ = pooled mean values ± standard deviations
** $p < 0.001$
† $p < 0.1$
†† $p < 0.03$
‡ $p < 0.25$
‡‡ $p < 0.02$

VARIABLES

VV: Volumetric density of bone (trabecular bone/total bone) in mm^3/cm^3.

SV: Surface density of bone (trabecular bone/total bone) in mm^2/cm^3.

D-TRAB: Mean trabecular diameter in microns.

SV-OB: Surface density of active osteoid covered by osteoblasts in mm^2/cm^3.

OBI: Osteoblastic index (number of osteoblasts/mm^3 of bone).

OCL%: Fraction of trabecular surface covered by osteoclastic interface (bone osteoclast interface/total trabecular surface) in per cent.

V-L-TOT: Relative volume density of total resorptive lacunae (volume of total resorptive lacunae/trabecular bone) in per cent.

OCI: Osteoclastic index (number of osteoclasts/mm^3).

FIB %: Fraction of trabecular surface covered by fibers (bone fiber interface/total trabecular surface) in per cent.

LEGENDS

FIGURE 0A. An end-view of the copolymer implant plug magnified 50X in a scanning electron microscope.

FIGURE 0B: The same implant as FIGURE 0A, but magnified 100X. The irregular, spongy morphology of the copolymer may be easily observed.

FIGURE 1. Osseous wound healing in a control site of the tibia of a rat at 28 days.

FIGURE 2A: At 7 days the copolymer implant plug (*) appeared wavy, heterogenous, and amorphous with infrequent lymphocytes and polymorphonuclear cells (arrows).

FIGURE 2B. At 7 days zones of osteoid with robust osteoblasts could be seen.

FIGURE 3. By 14 days within the experimental wound bed the copolymer had broken down into numerous islands (*). Bony trabeculae were evident throughout the dissolving implant (arrows). A bony bridge had also formed (arrowheads). An inflammatory response was not evident.

FIGURE 4: By 21 days numerous bony trabeculae were developed at the implant site and there was scarce evidence of the implant.

FIGURE 5: At 21 days all wound sites treated with an implant had a well developed bony bridge (arrowheads).

FIGURE 6: By 42 days complete obliteration of the osseous defect was achieved (between arrowheads). In several specimens, wound closure was demonstrated at 28 days. No inflammatory infiltrate was present.

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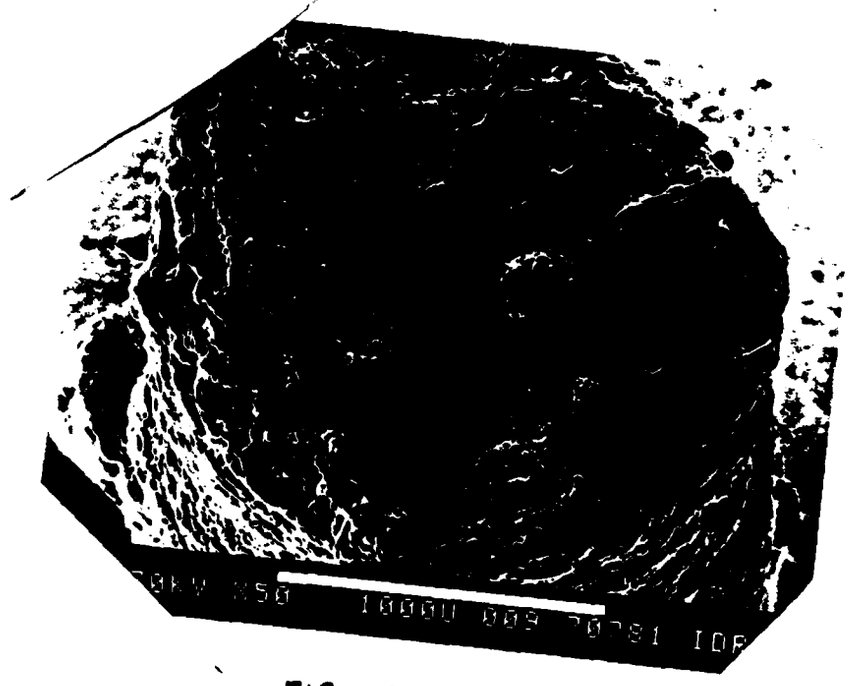

FIG. 8A

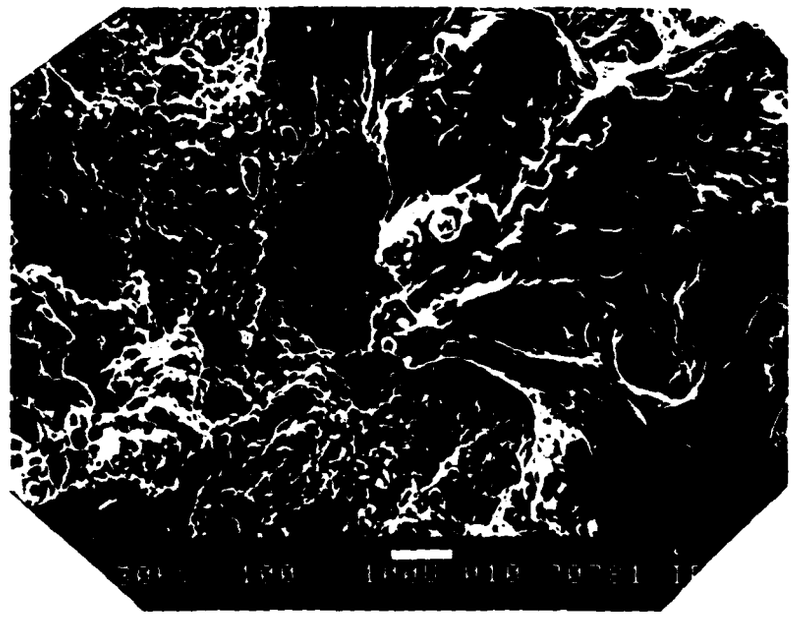

FIG. 8B

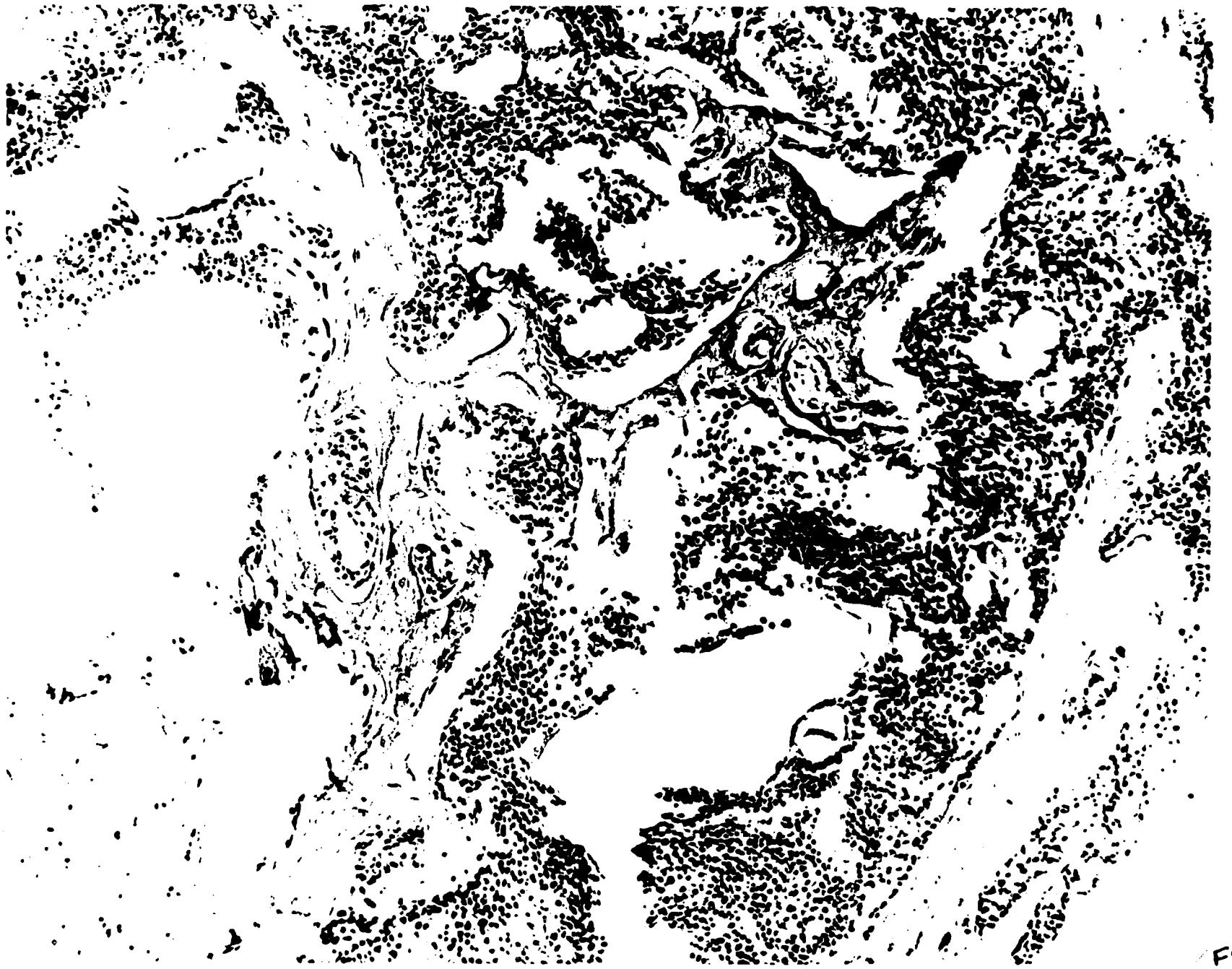

FIG. 1

FIG. 2 A

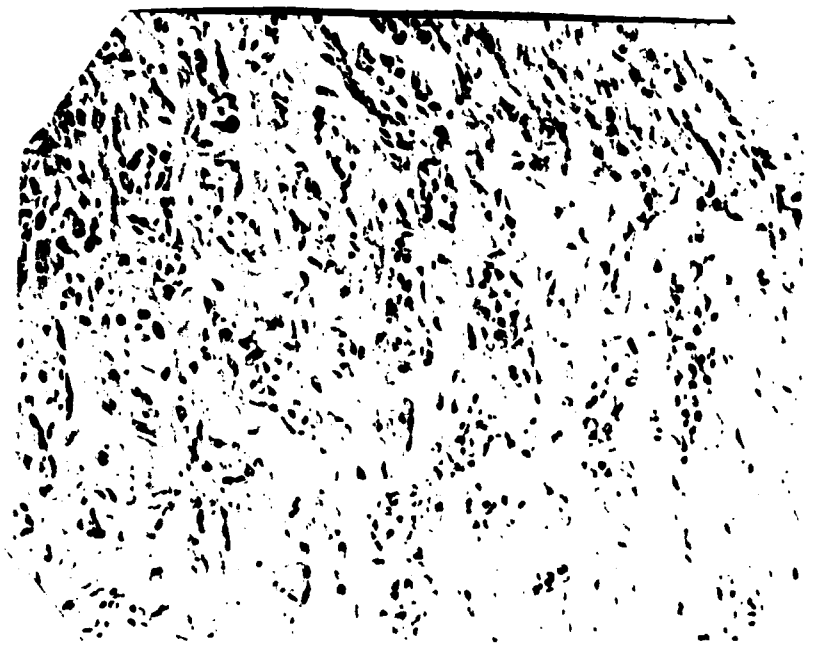

FIG. 2B

FIG. 3

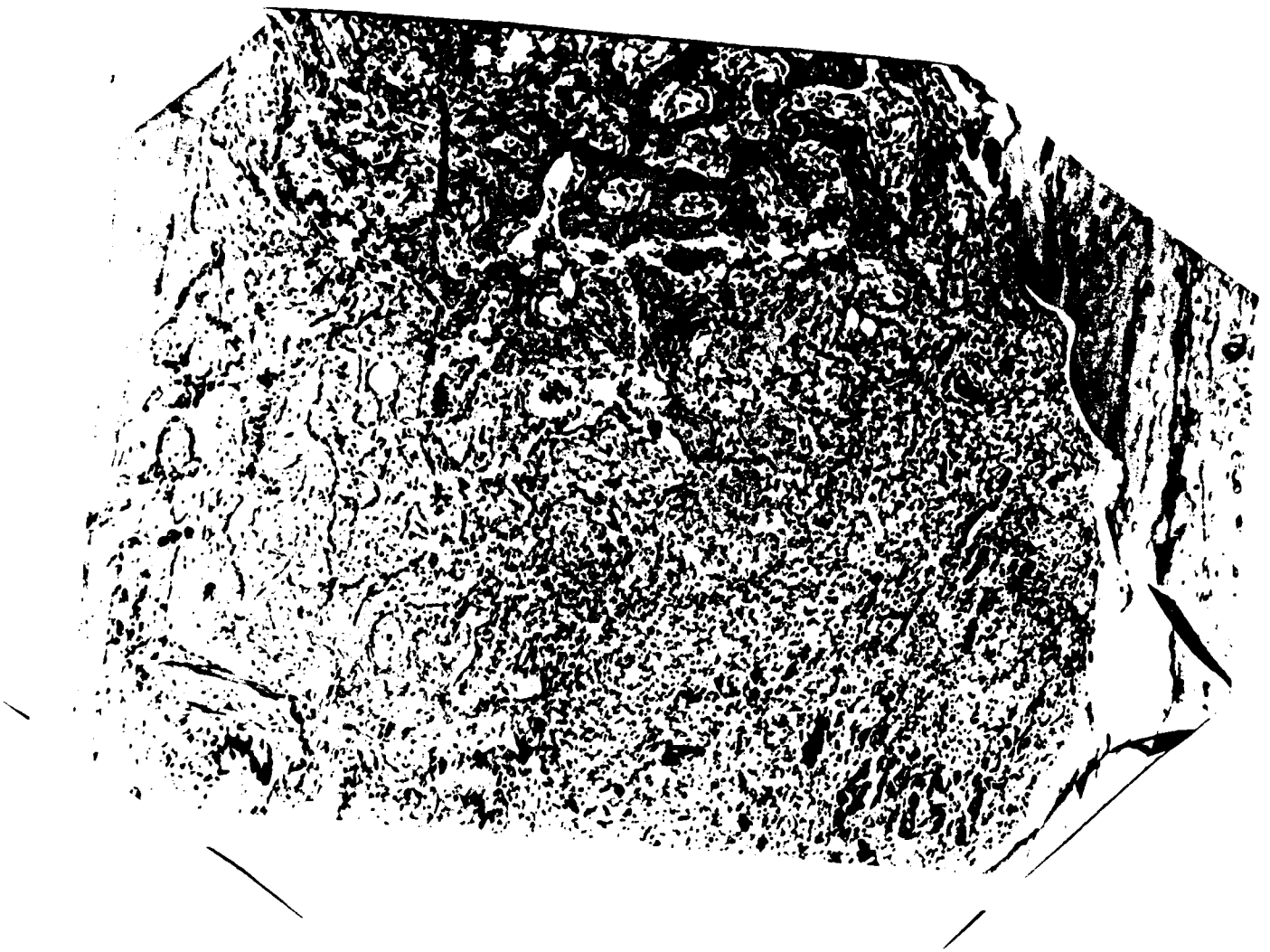

FIG. 4

FIG. 5

FIG. 6

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